

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**75609**

**CORRESPONDENCE**

ANDA 75-609

KV Pharmaceuticals  
Attention: Herbert G. Luther, Ph.D.  
2503 South Hanley Road,  
St. Louis, MO 63144-2555  
|||||||

APR 20 1999

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Doxazosin Mesylate Tablets, 1 mg, 2 mg, 4 mg  
and 8 mg

DATE OF APPLICATION: March 26, 1999

DATE (RECEIVED) ACCEPTABLE FOR FILING: March 30, 1999

We will correspond with you further after we have had the opportunity to review your application.

However, in the interim, please submit three additional copies of the analytical methods and descriptive information needed to perform the tests on the samples (both the bulk active ingredient(s) and finished dosage form) and validate the analytical methods. Please do not send samples unless specifically requested to do so. If samples are required for validation, we will inform you where to send them in a separate communication.

In addition, we note that while you have provided a comparison of your proposed package insert with that of the reference listed drug, you have failed to provide a container label for the reference listed drug. Labeling is defined in the regulations to include both container labels and package insert labeling. Please provide a container label for the reference listed drug per 314.94(a)(8).

Please identify any communications concerning this application with the number shown above.

Should you have questions concerning this application contact:

Bonnie McNeal  
Project Manager  
(301) 827-5848

Sincerely yours,

*/S/*

*for*

Robert L. West, M.S., R.Ph.  
Director,  
Division of Labeling and Program Support  
Office of Generic Drugs  
Center for Drug Evaluation and Research

ANDA 75-609  
cc: DUP/Jacket  
Division File  
HFD-82  
Field Copy  
HFD-330  
HFD-610/R.West  
HFD-615/MBennett

Endorsements: HFD-615/HGreenberg, Act. Chief, RSB  
HFD-615/SMiddleton, CSO *S. Middleton*  
HFD-623/VSayed, Sup. Chemistry/  
Word Document

*H. Greenberg* 4/20/89  
date

date *4/15/89*

date

ANDA Acknowledgment Letter!

**KV PHARMACEUTICAL COMPANY**

**Certified Mail**  
**ML No.**

August 23, 2000

Office of Generic Drugs,  
CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

**KV**

**ORIG AMENDMENT**

N/AF

**Re: ANDA 75-609**  
**Doxazosin Mesylate Tablets, 1 mg, 2 mg, 4 mg, and 8 mg**  
**LABELING AMENDMENT TO FAX AMENDMENT DATED 8/21/2000**  
**(Final Printed Label)**

Dear Madam/Sir:

Reference is made to our Fax Amendment dated August 21, 2000. The subject fax amendment included final printed labeling. After submitting this amendment, KV realized that a small typographical error had been made in the final printed product insert. In the Clinical Pharmacology section, Table 1, Study 2, a small square was superimposed the double asterisk of the "-5.0" within the chart. KV is including a new set of twelve (12) final printed inserts where this mistake was corrected. We apologize for any inconvenience, and trust that you will find everything else in order.

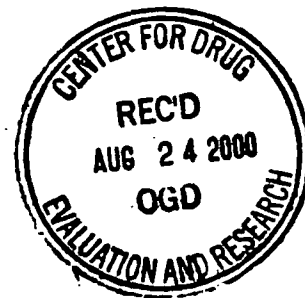
If any additional information is needed, please contact the undersigned at 314-645-6600, ext. 2535. Our fax number is 314-567-0704.

Sincerely,



Angel L. Rodriguez, RAC  
Regulatory Affairs Director

enclosures



**KV PHARMACEUTICAL COMPANY**  
Certified Mail  
ML No. 00/108

August 21, 2000

Office of Generic Drugs,  
CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

ORIG AMENDMENT  
NIFA

**KV**

Re: **ANDA 75-609**  
**Doxazosin Mesylate Tablets, 1 mg, 2 mg, 4 mg, and 8 mg**  
**FAX AMENDMENT (Chemistry, Bioequivalence, and Final Printed Label)**

Dear Madam/Sir:

Reference is made to our abbreviated new drug application date March 26, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for subject drug product and your facsimile dated August 14, 2000, with a request for some minor amendments to the submission.

Listed hereunder are the deficiencies noted in bold followed by our responses unbolded.

**CHEMISTRY**

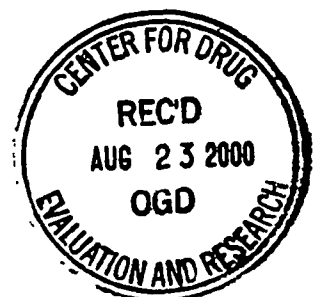
**A. Deficiencies:**

1. **Based on your results, the total impurities for the Doxazosin Mesylate drug substance should be further tightened.**

Response:

The specification for total impurities for the doxazosin mesylate drug substance was tightened to NMT %. The updated specifications for the active pharmaceutical ingredient can be found in attachment 1 of this submission.

2. **We disagree with you that a specification for total impurities is unnecessary under the current conditions (page 9 of the major amendment dated 2/9/00). The individual and total impurities of the Doxazosin Mesylate Tablets should be tested and monitored at each scheduled stability station. Please include the test and specifications of individual unknown, total unknown, and total impurities for the product release and stability.**



Office of Generic Drugs,  
CDER, FDA  
Document Control Room, Metro Park North II  
August 21, 2000

Response:

The drug product release and stability specifications for the proposed drug product were revised to include a specification for individual and total impurities (known and unknown). The specifications are as follows:

- Individual impurities – NMT     % for any single impurity.
- Total impurities – NMT     % for total impurities

A review of the available degradant data for the proposed drug product was conducted. It was determined that only 2 of the observed peaks (A and J) occurred at levels near     %. All other peaks were below     %. Hence, we recommend a specification of NMT     % total impurities. This specification considers the 2 peaks observed at levels between     % and potential raw material variances.

The updated specifications for the proposed drug product can be found in attachment 2 of this submission.

**3. The FDA Denver district laboratory has completed the method validation on the drug substance and the finished drug product. Please respond to the following comments:**

**(a) The equations for the % related compounds and dissolution tests for the finished product have a minor error. The equation shows the result taken times '**

Response:

The correction was made. The updated test method is included in attachment 3 of this submission.

**(b) The raw material method for related compounds utilizing the     procedure was satisfactory except for the use of reference solution II. On the     plate that the FDA Denver laboratory used, the spot was barely visible. You should switch from the     procedure to the finished product related compounds procedure for better accuracy of the impurities, especially since the methodology is already available.—**

Office of Generic Drugs,  
CDER, FDA  
Document Control Room, Metro Park North II  
August 21, 2000

Response:

The finished product related compounds procedure has been added to the active pharmaceutical ingredient test monograph. The procedure will be retained as an alternate method. The specification for related compounds for the procedure is the same as that of the procedure. The updated testing procedure can be found in attachment 4. In addition, KV expanded the validation of this method to cover it's application on the active drug substance. The corresponding report can be found in attachment 4.

**4. Your proposed specification of Q % in 45 minutes is not acceptable. The following in vitro dissolution testing should be incorporated into your manufacturing controls and stability program:**

**Apparatus: USP Apparatus II (paddle) at 50 rpm**  
**Medium: 900 mL of 0.01N Hydrochloride at 37°C**  
**Tolerance: NLT % (Q) in 30 minutes**

**Please provide stability data to demonstrate that your product meets these specifications.**

Response:

KV Pharmaceutical Company has revised its dissolution specification to Q % @ 30 minutes. Please refer to bioequivalency amendment dated June 9<sup>th</sup> for further details on dissolution testing. KV Pharmaceutical Company hereby commits to perform and evaluate all dissolution testing for this drug product as prescribed by the Agency on all dissolution testing subsequent to this amendment. The updated proposed drug product specifications can be found in attachment 2. The updated dissolution testing procedure is in attachment 3.

Attachment 5 contains dissolution results obtained from testing the product after being in room temperature conditions for 18 months. This was part of the data that was submitted to the Division of Bioequivalence in a Bio Amendment dated July 5<sup>th</sup>, 2000.

Office of Generic Drugs,  
CDER, FDA  
Document Control Room, Metro Park North II  
August 21, 2000

**B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:**

**Please submit available room temperature stability data.**

Response:

The updated stability reports for the proposed drug product application batches can be found in attachment 6. Please note the stability specification for this product does not reflect the actual changes requested in this amendment, as the stability testing had been conducted before hand. Also note that no stability data is provided for the unit dose packaging configuration. KV Pharmaceutical Company has decided not to market this packaging configuration at this time. Hence, at this time KV is withdrawing such packaging configuration from it's ANDA.

**BIOEQUIVALENCE:**

**The following *in vitro* dissolution testing should be incorporated into your manufacturing controls and stability program:**

**Apparatus: USP Apparatus II (paddle) at 50 rpm  
Medium: 900 mL of 0.01N Hydrochloride at 37°C  
Tolerance: NLT % (Q) in 30 minutes**

Response:

KV Pharmaceutical Company has incorporated the requested *in vitro* dissolution testing into our manufacturing controls and stability program. The updated proposed drug product specifications can be found in attachment 2. The finished product test procedure is in attachment 3.

**LABELING:**

1. **CONTAINER – bottles of 100 and 1000 tablets**  
**Left side Panel: revise the “Each tablet contains....”statement to read as follows:**

**“Each tablet contains Doxazosin Mesylate equivalent to xx mg doxazosin.  
[lower case “doxazosin mesylate”]**

Office of Generic Drugs,  
CDER, FDA  
Document Control Room, Metro Park North II  
August 21, 2000

2. **CARTON – Unit dose cartons of 100**  
**Front panel: revise the “Each tablet contains....”statement to read as follows:**

**“Each tablet contains doxazosin mesylate equivalent to xx mg doxazosin.  
[make “tablet” singular and utilize lower case “doxazosin mesylate”]**

3. **UNIT-DOSE BLISTERS**  
**Satisfactory in draft as of the February 8, 2000 submission**

4. **INSERT**  
**a. CLINICAL PHARMACOLOGY**

**Table 1, Study 2 –**

**Revise to include an asterisk where indicated by the reference listed drug to be in accordance.**

**b. PRECAUTIONS**

**Drug Interactions; first paragraph, second sentence –**

**...indicate that doxazosin has.... [spelling “doxazosin”]**

5. **PATIENT PACKAGE INSERT**  
**Satisfactory in draft as of the March 28, 1999 submission.**

**Please revise your labels and labeling, as instructed above, and submit in final print.**

As per your request, all changes noted above in labeling deficiencies have been made and we are herewith submitting 12 copies of final printed labeling for the containers, insert, and patient package insert for all dosage strengths.


KV Pharmaceutical hereby withdraws information regarding unit dose packaging of the drug product from the **HOW SUPPLIED** section of the labeling without prejudice, due to a lack of marketing interest. If, at a later date, this marketing interest changes, the final printed labeling for this container closure will be submitted.

Page No. 6

Office of Generic Drugs,  
CDER, FDA  
Document Control Room, Metro Park North II  
August 21, 2000

As per requirements, we hereby certify that a true copy of the CMC amendment portion of this deficiency has been sent to our St. Louis Area Office to be incorporated into the original ANDA submission. If any additional information is needed, please contact the undersigned at 314-645-6600, ext. 2535. Our fax number is 314-567-0704.

Sincerely,



Angel L. Rodriguez, RAC  
Regulatory Affairs Director

/fmc

enclosures

cc: FDA, St. Louis Area Office

**KV PHARMACEUTICAL COMPANY**

**NDA ORIG AMENDMENT**

*N/AB*



July 5, 2000

Office of Generic Drugs, CDER, FDA  
Document Control Room, MPN - II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

**RE: ANDA 75-609 Doxazosin Mesylate tablets, 1-mg, 2-mg, 4-mg, 8-mg.  
Telephone Amendment (Bioequivalence)**

Dear Sir or Madam:

Reference is made to a telephone conversation held between K. Scardina, J. Fan, and C. Chaurasia, from FDA and H. Luther and the undersigned from KV Pharmaceutical Company (KV). The call was made on June, 26, 2000.

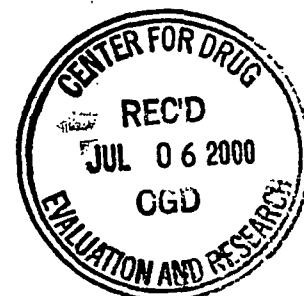
KV hereby submits the following Telephone Amendment, providing new dissolution profiles from the KV Doxazosin Mesylate Tablet batches submitted in ANDA 75-609. The profiles were generated using the updated dissolution test procedure, as described in our bioequivalence amendment dated June 9<sup>th</sup>, 2000. The profiles are as follows:

Percent dissolved (%) per X minutes																
	1-mg R366081				2-mg R376009				4-mg R366082				8-mg R366093			
T1																
T2																
T3																
T4																
T5																
T6																
avg	90	94	95	97	81	84	87	91	85	91	93	95	91	97	99	99
SD	6.8	2.1	1.7	1.3	3.8	3.6	3.9	2.9	6.4	3.5	3.2	1.8	6.3	2.1	0.8	0.5

Should you require further information, do not hesitate to contact us at your earliest convenience. Thanks.

Cordially,

Angel L. Rodriguez, RAC  
Regulatory Affairs Director



**KV PHARMACEUTICAL COMPANY**

**ORIG AMENDMENT**

N/AB



June 9, 2000

Office of Generic Drugs, CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

**RE: ANDA 75-609 Doxazosin Mesylate Tablets, 1 mg, 2 mg, 4 mg, and 8 mg.  
Bioequivalency Amendment**

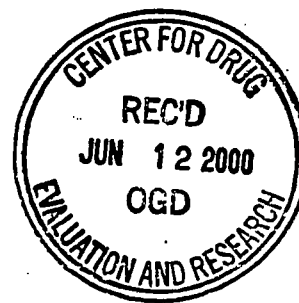
Dear Sir/Madam:

KV Pharmaceutical Company hereby submits this bioequivalency Amendment to our ANDA 75-609, Doxazosin Mesylate Tablets, 1 mg, 2 mg, 4 mg, and 8 mg. This submission is in response to FDA's fax communication dated April 24, 2000. In this communication you forwarded to us the following observation:

*"Your results showed that there was approximately % lower dissolution for the 2-mg and 4-mg strengths. Since the formulations of doxazosin 2-mg and 4-mg tablets are similar to those of the 1-mg, and 8-mg tablets, respectively, please explain the variability observed in the % dissolution values across and within the strengths of doxazosin mesylate tablets especially those of the 2-mg and 4-mg strengths compared to the 1-mg strength that underwent bioequivalence testing."*

The variability observed in the % dissolution values across and within the strengths of doxazosin mesylate tablets is due to slight variations in the actual Hydrochloric Acid (HCl) normality of the dissolution media used. An HCl normality range from produces dissolution results with greater than % difference. The source of this variability was traced to the way the analytical method was written. The analytical method required the preparation of a HCl dissolution media. However, it did not state the specific normality of HCl to use to prepare the final target normality of HCl dissolution media. Hence, analytical chemists were using either concentrated, while preparing the diluted

The viscosity of the HCl is dependent upon its concentration. This caused slight variances in the pipetted acid volumes. This fact along with the difference in starting acid concentrations, produced the mentioned variability in dissolution media normality. This was the cause of the variability observed in the percent dissolution values across and within the strengths of Doxazosin Mesylate.



KV has improved the method to clearly indicate that the HCl Media will be made out of standardized HCl. Further, KV is including a new set of dissolution data for each strength, following the corrective actions to the method.

900 ml, 0.01 N HCl, 50 rpm @ 45 min				
	1-mg	2-mg	4-mg	8-mg
Tablet #1	%	%	%	%
Tablet #2	%	%	%	%
Tablet #3	%	%	%	%
Tablet #4	%	%	%	%
Tablet #5	%	%	%	%
Tablet #6	%	%	%	%
Average	89%	84%	85%	85%
SD	5.0	2.9	1.9	3.6

It is KV's point of view that the above listed data further supports the adequacy of our proposed dissolution specification for this immediate release drug product. (Q % @ 45 min). Should you require further information on this respect, do not hesitate to contact either Dr. Herbert G. Luther at 314-645-6600, ext. 2530, or the undersigned at ext. 2535.

Cordially,



Angel L. Rodriguez, RAC  
Director Regulatory Affairs

# KV PHARMACEUTICAL COMPANY

CERTIFIED MAIL  
ML NO. 00/008

February 9, 2000

OFFICE OF GENERIC DRUGS, CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

**KV**

**NEW CORRESP**

Nc

Re: ANDA 75-609  
Doxazosin Mesylate Tablets, 1 mg, 2 mg, 4 mg, and 8 mg  
FDA MAJOR AMENDMENT VIA FACSIMILE

Dear Sir/Madam:

Reference is made to our abbreviated new drug application dated March 26, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for subject drug product and your facsimile dated October 19, 1999 with a request for some major amendments to the submission.

Listed hereunder are the deficiencies noted in bold followed by our response unbolded.

## CHEMISTRY

### A. Deficiencies:

1. The specification of the melting range listed as "report" is not acceptable. Please specify the limit of melting range for the Doxazosin Mesylate drug substance.

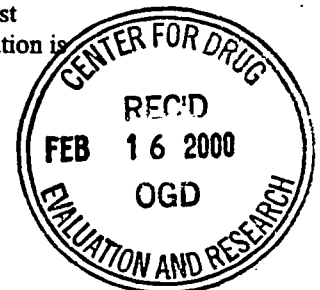
KV will accept and has incorporated the supplier's specification of NLT for melting range for the Doxazosin Mesylate drug substance. The updated testing method and specifications for the active drug substance are included in this amendment in exhibit #1.

2. Please provide the laboratory operating procedure entitled "melting range determination".

KV has adopted the supplier's methodology to conduct the melting range determination for the drug substance. An outside laboratory will perform this test for KV Pharmaceutical. Attached in exhibit #2 you will find a copy of the method along with the necessary cGMP certification and debarment notification from this outside contract laboratory.

3. Please include the test and specification of the loss on drying for the Doxazosin Mesylate drug substance.

As per your request a test for loss on drying has been included in the test method for the drug substance. A specification of NMT % has been established based on the current specification for water (0.5%), total residual solvents (1,500 ppm or 0.15%), and assay (on anhydrous basis) of the active (%). Please see exhibit #1 for the updated active drug substance test method. A copy of the laboratory operating procedure used for Loss on Drying Determination is included in exhibit #3.



OFFICE OF GENERIC DRUGS.

CDER/FDA

ANDA 75-609

Doxazosin Mesylate Tablets, 1 mg, 2 mg, 4 mg, & 8mg

FDA MAJOR AMENDMENT VIA FACSIMILE dated October 19, 1999

4. Please include the test and specification of the organic volatile impurities for the Doxazosin Mesylate drug substance.

For the test and specifications of the organic volatile impurities, KV will accept the results from the supplier, In exhibit #4 they have certified that to their knowledge no potential for the OVI's listed in current USP <467> to be present

5. Please include the test and specification of particle size of the Doxazosin Mesylate drug substance.

The particle size specification for the drug substance is NMT % determined via . has been included in the revised analytical testing method for the drug substance. Please see exhibit #1. A copy of the laboratory operating procedure for Particle Size Determination is included in exhibit #5 and information regarding the supplier's specifications for sieve analysis is also included in this exhibit.

6. Please include the limit of the total unknown impurities for the Doxazosin Mesylate drug substance.

A limit of NMT % for the total unknown impurities has been established for the Doxazosin Mesylate drug substance and is included in the revised analytical test method for the drug substance in exhibit #1.

7. Please include the identification test for substance. for the Doxazosin Mesylate drug substance.

method will be used as the identification test for and will be performed by the outside laboratory, We have included a copy of the method in exhibit #2. The manufacturer has advised that there are several distinct forms of anhydrous Doxazosin mesylate and the three important ones can easily be differentiated by The maxima of the three are approximately 262°C, 270°C, and 277°C. KV will be using the highest By means of , which is used to assess melting range, KV can also control the of the Laboratory results from the outside laboratory are included in exhibit #6 along with information from the drug substance manufacturer.

8. Please include the sample size for the test in your master production and control records. We recommend that the sample size of the blend material be not greater than three times the weight of an individual dose.

Please note that in each of the master production and control records (pages 2929, 3022, 3117, and 3207) submitted for the intended production batches, a 0.35 cm<sup>3</sup> unit dose sampler was noted to be used for blend sampling of the 1 mg and 2 mg strengths. A 0.75 cm<sup>3</sup> unit dose sampler was noted to be used for the blend sampling of the 4 mg and 8 mg strengths. For each case, the unit dose sampler specified will yield a sample equivalent to NMT three times the unit dose weight. Please see exhibit #7 for the master production and control records.

9. The master formulas of the subject product do not show any sampling instructions for routine test. Please provide the sampling plan (established SOP) of the final blend for the test.

February 9, 2000

OFFICE OF GENERIC DRUGS,  
CDER/FDA  
ANDA 75-609

Doxazosin Mesylate Tablets, 1 mg, 2 mg, 4 mg, & 8mg  
FDA MAJOR AMENDMENT VIA FACSIMILE dated October 19, 1999

Sampling instructions for tests were included in the proposed master formulas that were a part of the original submission on pages 2929, 3022, 3117, and 3207. For each drug product that requires testing, the master formulas will contain the sampling procedures and sample size; acceptance criteria; and analytical procedure for evaluation of results. These steps are designed to comply with cGMP requirements as delineated in 21 CFR 211.110(a). A separate standard operating procedure has been revised and is included in exhibit #8.

10. In the proposed product specification for Doxazosin Mesylate Tablets (p. 3815), the analytical method should be specific. The updated version should be used, for example, method instead of method .

Page 3815 has been revised to include the specific analytical method that is in use at this time for the testing of the finished drug product. Also the product specifications for the drug product have been revised to include the proposed specifications included in this response. Please see exhibit #9.

11. In the dissolution testing, 900 mL 0.01N HCl, 50 rpm should be used. The specification of the Doxazosin Mesylate tablet dissolution should be NLT % in 30 minutes. Please follow the method and procedures for conducting the dissolution test of the Doxazosin Mesylate tablets recommended by the Division of Bioequivalence, Office of Generic Drugs (see attached).

KV Pharmaceutical Company (KV) has evaluated the proposed dissolution specifications. Based on data from the ANDA batches, the reference product, and data generated following current FDA guidance, KV believes the specification of NLT % @ 30 minutes using 50 RPM is not appropriate for our proposed product. KV wants to re-emphasize that the in-vivo results included in the original application demonstrate bioequivalence between the reference product and the KV product.

As part of our evaluation of a suitable dissolution test and specification, KV performed multiple dissolution studies on both our proposed product and the reference product. Single point dissolution and multiple point dissolution profiles were conducted. Our data was generated from the following batches:

Strength	Cardura batch no.	KV batch no.
1-mg	9EP012A	R366081
	7EP043A	
2-mg	7EP053A	R376009
4-mg	7EP056A	R366082
8-mg	7EP057A	R366093

February 9, 2000

OFFICE OF GENERIC DRUGS,

CDER/FDA

ANDA 75-609

Doxazosin Mesylate Tablets, 1 mg, 2 mg, 4 mg, & 8mg

FDA MAJOR AMENDMENT VIA FACSIMILE dated October 19, 1999

✓ The proposed FDA single point release testing was performed on KV batches in all packaging configurations. The data is as follows:

900 mL, HCl 0.01N, Paddle, 50 RPM, Q      % @ 30 MIN												
Sample	Strength											
	1-mg			2-mg			4-mg			8-mg		
	100's	1000's	Blister	100's	1000's	Blister	100's	1000's	Blister	100's	1000's	Blister
T1												
T2												
T3												
T4												
T5												
T6												
Avg	82	76	75	68	59	61	66	68	69	75	75	77
SD	4.2	2.1	3.1	3.4	2.8	2.3	2.5	3.9	3.3	5.1	2.4	2.8

Based on FDA's proposed specification of Q % @ 30 minutes, the Stage 1 specification would be "Each of 6 units not less than %". Our ANDA batch data reflects that 52 values out of 72 (72%) do not meet the proposed criteria. The 52 values are identified in bold in the above table.

KV's position is based on three points:

Point 1: A higher than % rate of stage 2 dissolution release testing frequency is excessive and counter-productive. The following items in *italic* are some excerpts from HUMAN DRUG cGMP NOTES, March 1996.

*"Is dissolution testing past the Stage 1 level significant enough to be cited on FDA-483s?"*

*"The Center has received several inquiries from industry regarding the interpretation of dissolution specifications as outlined in the USP general chapter on Dissolution <711> [and the chapter on Drug Release <724>]. The inquiries stemmed from FDA-483 observations issued by field investigators citing dissolution testing past the Stage 1 (S1) level as indications of product failure and/or lack of process control. This has prompted several pharmaceutical companies to ask the Agency to set "wider" dissolution specifications which will allow all batches manufactured to pass at the S1 level...*

*...Similar situations have come to this division's attention by way of regulatory case review, where, as part of the GMP violations cited, 483 observations such as "Lack of failure investigation(s) for lot(s) ... which failed dissolution testing at the S1 level." or "Lack of process control for ...product due to dissolution failure at the S1 level." are made..."*

If the percentage of Stage 2 tests is significantly high, KV will be susceptible to the issues illustrated above. The cGMP notes continue to state:

*"...Depending on the context of the occurrence of dissolution testing past the S1 level, other 483 observations would be more appropriate. For example, if a large percentage of all batches manufactured, within a specific period, have to be tested past the S1 level, a more appropriate 483 observation would be "Failure to determine why batches manufactured during this specific period had to be tested through to S2 or S3." Another example is if a large percentage of batches manufactured suddenly have to be tested through S2 or S3, after only rarely having to be tested past S1; a more appropriate observation would be "Failure to determine why a majority of*

February 9, 2000

OFFICE OF GENERIC DRUGS,

CDER/FDA

ANDA 75-609

Doxazosin Mesylate Tablets, 1 mg, 2 mg, 4 mg, & 8mg

FDA MAJOR AMENDMENT VIA FACSIMILE dated October 19, 1999

*recently manufactured batches now have to be tested through to S2 or S3." Such observations could be made assuming that: 1> Initial dissolution testing for the product in question only rarely proceeded past S1 and is now always proceeding to S2 or S3; and, 2> The firm failed to recognize the possibility of a process or testing problem by this change in the dissolution profile of its product."*

A high rate of Stage 2 testing would inhibit the sensitivity for monitoring possible changes that might only be seen by an increase in Stage 2 testing frequency, as suggested above.

**Point 2: Out of Specification results at the FDA proposed one-point dissolution criteria do not translate to in-vitro in-equivalence.**

To demonstrate in-vitro equivalence between the reference and KV product, new dissolution profiles with the proposed dissolution conditions were performed. For the 1-mg strength, a second batch of Cardura was analyzed, as the reference product for the bio study had expired. To accompany the new Cardura batch, the KV bio batch was analyzed again on the same day the new batch was analyzed.

**900 mL, HCl 0.01N, Paddle, 50 RPM (average of 6 values)**

Sample (Min)	1-mg				2-mg		4-mg		8-mg	
	Old Profile		New Profile		Cardura	KV	Cardura	KV	Cardura	KV
	Cardura	KV	Cardura	KV						
10	81	79	77	85	76	66	68	75	74	76
20	88	82	82	86	84	72	73	78	78	81
30	90	83	83	89	87	<b>77</b>	<b>76</b>	<b>80</b>	81	<b>81</b>
45	91	84	86	91	89	<b>79</b>	<b>77</b>	83	83	<b>82</b>
60	92	85	88	92	90	<b>81</b>	<b>79</b>	86	81	<b>82</b>

The average numbers in bold contain individual values which fall outside the FDA proposed specification. The data demonstrates that the single point release criteria may fall outside Stage 1, while the profile remains comparable to the reference product. Further, the data also demonstrates the reference product has incidence of stage 1 noncompliance.

To demonstrate that the dissolution profile has not changed since the ANDA batches were manufactured, the originally proposed dissolution profile test procedure was conducted on the aged KV 1-mg batch (bio-batch). The results are as follows (shaded values are from the ANDA product tested on 2/2/2000):

**900 mL, HCl 0.01N, Paddle, 75 RPM**

Sample (Min)	1-mg		
	Cardura	KV	
15	97	100	92
30	97	99	96
45	98	101	95
60	96	101	93
F2		58.9	

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Stability studies conducted on the product at room temperature also reflect aging has no effect upon dissolution:

900 mL, HCl 0.01N, Paddle, 75 RPM, Q @ 45 MIN							
1-mg		2-mg		4-mg		8-mg	
T <sub>0</sub>	T <sub>12</sub>	T <sub>0</sub>	T <sub>12</sub>	T <sub>0</sub>	T <sub>12</sub>	T <sub>0</sub>	T <sub>12</sub>
97%	89%	84%	94%	90%	93%	96%	100%

Point 3: OGD can approve dissolution specifications that may be different from the reference drug product.

Guidance to Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms, dated August, 1997, also specifies:

*"In the case of a generic drug product, the dissolution specification are generally the same as the reference listed drug (RLD). The specifications are confirmed by testing the dissolution performance of the generic drug product from an acceptable bioequivalence study. If the dissolution of the generic product is substantially different compared to that of the reference listed drug and the in vivo data remain acceptable, a different dissolution specification for the generic product may be set."*

Therefore, KV proposes the following one point dissolution criteria:

This newly proposed specification falls between KV's original proposal and FDA's position, and does not pose an unreasonably high percentage of stage 2 or 3 testing for release.

12. Please include the testing in the master formulas as a process control test for the routine production of the Doxazosin Mesylate Tablets, 1 mg, 2 mg, 4 mg, and 8 mg. We recommend that acceptance criteria for the analysis be set as % (mean of individual results) with a RSD NMT %.

sampling and testing was included on pages 2929, 3022, 3117, and 3207 respectively. The in-process specifications found in the master batch records for the drug product have been revised to include (See exhibit #7) The acceptance criteria for the is set as % (mean of individual results) with a RSD of NMT % as was submitted on pages 3563, 3565, 3567, and 3569 in the original submission.

13. The in-process specifications on pages 3563, 3567, and 3569 should be incorporated into the master batch record for the routine production of the Doxazosin Mesylate Tablets, 1 mg, 2 mg, 4 mg, and 8 mg.

The in-process specifications were incorporated into the master batch record for the routine production of Doxazosin Mesylate Tablets with the exception of as stated above.



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16. Specification for individual and total degradants/impurities should be set for the product release and stability for all strengths.

The ANDA submission batches exposed to different storage conditions were assayed for the eleven impurities listed above. Samples analyzed were as follows:

Tablet Strength (Lot No.)	Storage Time & Conditions	Package Configuration
1 mg (R366-081)	3 mo. at 40C/75% RH	100's, 1000's, blister package
	12 mo. at Room temp.	100's, 1000's, blister package
2 mg (R376-009)	3 mo. at 40C/75% RH	100's, 1000's, blister package
	12 mo. at Room temp.	100's, 1000's, blister package
4 mg (R366-082)	3 mo. at 40C/75% RH	100's, 1000's, blister package
	12 mo. at Room temp.	100's, 1000's, blister package
8 mg (R366-093)	3 mo. at 40C/75% RH	100's, 1000's, blister package
	12 mo. at Room temp.	100's, 1000's, blister package

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Results are provided in exhibit #14. These results show that none of the unknown impurities were present at a level above %.

Samples of the reference product (Cardura®) were also assayed for the same unknown impurities. The batches tested were from lots that had expired. Samples tested were as follows:

Tablet Strength	Lot No.	Product history (lot expiration date)
1 mg	5EP018A	November, 1997
	6EP003A	March, 1998
	K944A*	October, 1996
2 mg	K944A*	October, 1996
4 mg	K944A*	October, 1996
8 mg	7EP015A	November, 1999

\*The three dosage strengths were packaged as physician samples on blister cards under the same lot number.

Results from these analyses are provided in exhibit #15. These results show that none of the unknown impurities were present at a level above %.

Based on these studies, it is concluded that the presence of any known impurity above % is unlikely. Therefore, a specification of NMT % for any single known impurities is hereby being proposed for release and stability.

A specification for total impurities is unnecessary under the current conditions. There are no known impurities to report or add. In accordance with the Guidance for Industry ANDAs: Impurities in

Drug Substances, - Levels of impurities that are present but are below the validated limit of quantitation need not be reported and values between 0.05 and 0.09 should not be rounded to 0.1 percent in determining whether to identify the impurities. Hence, the addition of unknown impurities is not feasible because there will be no multiple impurities results to add.

To reconfirm the conclusions presented in this amendment, KV will monitor peaks at  $10^{-2}$  levels for the first 3 commercial batches as a part of RT stability studies. In the event that any impurity is found to exceed the % specification, that impurity will be identified and a prior approval supplement will be submitted to the Agency as per the recommendations in the current guidance.

The updated analytical method for the drug product, (#8445.10) which includes testing for the related compounds is provided in exhibit #16. The analytical validation for analysis of related compounds is included in exhibit #17. In exhibit #18 you will find revised stability protocols incorporating all of the revisions to the drug product specifications for each dosage strength.

17. Please include the identification test for Mesylate counter ion for the Doxazosin Mesylate drug substance.

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An identification test for Mesylate counter ion for the Doxazosin Mesylate drug substance has been done and is included herewith in exhibit #1 of the revised analytical test method. We are including in exhibit #19 information received from the drug substance manufacturer regarding the identification testing for the mesylate counterion.

18. Based on the actual result obtained, please tighten the limit of the total impurities for the Doxazosin Mesylate drug substance.

Based on results obtained, we have tightened the limits of the total impurities to NMT % for the Doxazosin Mesylate drug substance.

19. Please include the specification of moisture content for the release of Doxazosin Mesylate tablets.

We have included a specification of NMT % for moisture content for release of the drug product. The justification for this specification is based on data found in exhibit #20.

- B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The firms referenced in your ANDA application relative to the manufacturing and testing of the product must be in compliance with cGMPs at the time of approval.

We have noted and do acknowledge that the firms referenced in subject ANDA application relative to the manufacturing and testing of the drug product must be in compliance with cGMPs at the time of approval of the application.

2. The FDA district office will be performing method validation on the drug substance and the finished drug product. Please submit samples promptly when so requested.

We have noted and do acknowledge that the FDA district office will be performing method validation on the drug substance and the finished drug product. Samples have been submitted for method validation as requested to the FDA Denver District Office on December 9, and December 20, 1999. Please see copies of the transmittal letters in exhibit #21

3. Bioequivalence of your product with the innovator product has not been established.

We have noted and do acknowledge that bioequivalence of the drug product that is the subject of this application with the innovator has not been established and reviews of the studies to support the bioequivalence are still pending with the agency.

February 9, 2000

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**BIOEQUIVALENCE DEFICIENCIES:**

1. You have submitted frozen stability data only for 35 days. It is to be noted that the maximum storage time for the plasma samples was 60 days.

We are enclosing additional stability data to support the bioequivalence studies. Please see exhibit #22  
The data was generated by the analytical laboratory, The 71 day stability data was  
generated during the bioequivalence studies and the 1 year data was just completed.

2. You have used a rotation speed of 75 rpm in your dissolution testing for 1, 2, 4, and 8 mg Doxazosin Mesylate tablets, as opposed to the Agency's recommended speed of 50 rpm. You are advised to conduct dissolution studies using the Agency's recommended method described below.

Medium: 900mL, 0.01 N HCl at 37 °C

Apparatus: USP Apparatus 2 (paddle), 50 rpm

Sampling Time points: 10, 20, 30, 45, and 60 minutes

As per your request, we have conducted the dissolution studies using your recommended method described above and this information can be found in our response to #11 under the Chemistry deficiency response.

3. You have not submitted expiration dates for the innovator's Cardura® 2, 4, and 8 mg tablets used in the dissolution testing.

This information was submitted in the original application on page 000274 and we are herewith resubmitting it as per your request.

<u>Drug Product</u>	<u>Lot No.</u>	<u>Expiration Date</u>
Cardura® Tablets, 1 mg	7EP043A	12/1999
Cardura® Tablets, 2 mg	7EP053A	1/2002
Cardura® Tablets, 4 mg	7EP056A	1/2002
Cardura® Tablets, 8 mg	7EP057A	2/2002

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### LABELING DEFICIENCIES

#### 1. CONTAINER – bottles of 100 and 1000 tablets

- i. Front Panel: Revise to read – [add an asterisk]

Doxazosin Mesylate  
Tablets

X mg\*

- ii. Left Side Panel: Revise to read as follows –

\*Each tablet contains Doxazosin Mesylate equivalent to xx mg Doxazosin.

- iii. Please assure that the established name and expression of strength are the most prominent print on the label.

- iv. Front Panel: Please clarify what "ETHEX" represents. If it is a manufacturer, packager, or distributor, it must be labeled to be in accordance with CFR 201.1 (h) (5). Please revise and/or comment.

#### 2. CARTON – Unit-dose cartons of 100

- i. Front Panel and Side Panels – Revise to read – [add and asterisk]

Doxazosin Mesylate  
Tablets

X mg\*

- ii. Front Panel – revise to read as follows –

\*Each tablet contains Doxazosin Mesylate equivalent to xx mg Doxazosin.

- iii. See comment 1.(iv.) listed above.

#### 3. UNIT-DOSE BLISTER LABELS

Revise to read as follows –

Doxazosin Mesylate Tablets

X mg\*

#### 4. INSERT

##### a. DESCRIPTION

- i. First paragraph, third sentence – revise to read as follows:

The molecular formula for Doxazosin.. [replace with "molecular"]

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Doxazosin Mesylate Tablets, 1 mg, 2 mg, 4 mg, & 8mg  
FDA MAJOR AMENDMENT VIA FACSIMILE dated October 19, 1999

- ii. Second paragraph, second sentence – revise to read as follows:

Each Doxazosin Mesylate tablet (colored), for oral administration, contains ...

- iii. Third paragraph, first sentence – revise to read as follows:

In addition, each Doxazosin Mesylate tablet contains the following inactive ingredients:  
lactose....

**b. CLINICAL PHARMACOLOGY**

- i. Table 1 – Study 1 & Study 2: Revise to read “Doxazosin Mesylate” throughout the text.

- ii. Table 1 – Study 2: Revise as follows:

- iii. Replace with “Doxazosin” throughout the text except when referring to a specific dose.

**c. INDICATIONS AND USAGE**

- i. Benign Prostatic Hyperplasia (BPH) – First sentence – Revise to read as follows:

Doxazosin Mesylate tablets are indicated...

- ii. Hypertension – First sentence – revise to read:

Doxazosin Mesylate tablets are also indicated...

**d. CONTRAINDICATIONS**

Doxazosin Mesylate tablets are contraindicated...

**e. PRECAUTIONS**

Pediatric Use – revise to read:

...have not been established in pediatric patients.

**f. DOSAGE AND ADMINISTRATION**

Replace with “Doxazosin Mesylate tablet” throughout the text.

**g. HOW SUPPLIED**

- i. Second paragraph –

Please revise your tablet description throughout this section to be the same as you tablet descriptions found in your Controls for Finished Dosage form section. (to read as follows)

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CDER/FDA  
ANDA 75-609

Doxazosin Mesylate Tablets, 1 mg, 2 mg, 4 mg, & 8mg  
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Doxazosin Mesylate tablets are available as:

1 mg, gray, capsule-shaped tablets, debossed "ETH266" on one side and, "1", bisect, "mg", on the other side.

2 mg, yellow,...

- ii. We encourage you to relocate the "Rx only" statement to the Title section of the package insert.

#### 5. PATIENT PACKAGE INSERT

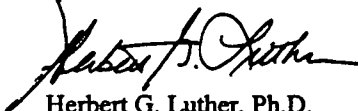
Satisfactory in draft as of March 26, 1999 submission.

Please revise your labels and labeling, as instructed above, and submit in final print or draft if you prefer.

All changes noted above for the container labels and insert labeling have been made and we are herewith submitting 4 draft copies each of the revisions along with an electronic submission for the same. Please see exhibit #23.

As per requirements, we hereby certify that a true copy of the CMC amendment portion of this deficiency has been sent to our St. Louis Area Office to be incorporated into the original ANDA submission. If any additional information is needed, please contact the undersigned.

Sincerely,



Herbert G. Luther, Ph.D.  
Vice President,  
Regulatory and Clinical Affairs

/fmc

enclosures

cc: FDA, St. Louis Area Office

**KV PHARMACEUTICAL COMPANY**

*ack for filing  
S. Middle (Lefu)  
4/13/99*



March 26, 1999

Office of Generic Drugs  
Center for Drug Evaluation & Research  
Food and Drug Administration  
Metro Park North  
7500 Standish Place, Room 150  
Rockville, MD 20855

**Re: Original ANDA Submission  
Doxazosin Mesylate Tablets, 1 mg, 2 mg, 4 mg and 8 mg**

Dear Director, Office of Generic Drugs:

KV Pharmaceutical Company is submitting herewith an original abbreviated new drug application seeking approval to market Doxazosin Mesylate Tablets, 1 mg, 2 mg, 4 mg and 8 mg. This drug product is bioequivalent to the listed drug, Cardura<sup>®</sup>, manufactured by Pfizer, Inc. pursuant to NDA 19-668.

This application is provided both as an archival copy and a review copy. The archival copy is contained in blue binders and consists of nine (9) volumes. The review copy is divided into two parts. The chemistry, manufacturing and controls part of the review copy is contained in red binders and consists of four (4) volumes. The bioequivalence part of the review copy is contained in orange binders and consists of six (6) volumes.

**This submission contains a Bioequivalence electronic submission ESD**

KV Pharmaceutical Company hereby declares that the data and information contained in the electronic submission is identical to the data and information contained in the paper copy of the ANDA, unless otherwise noted in the companion document on the diskette. Two copies of the bioequivalence ESD are contained in the archival copy of the ANDA immediately following this letter.

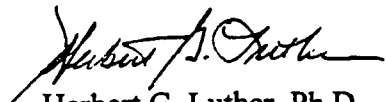
This letter also certifies that, concurrently with the filing of this ANDA, a true copy of the technical sections of the ANDA (including a copy of the 356H form and a certification that the contents are a true copy of those filed with the Office of Generic Drugs) is being sent to the St. Louis, Missouri District Office. This "field copy" is contained in burgundy folders.

**RECEIVE**

MAR 30 1999

Your earliest acknowledgement of this application will be greatly appreciated. If you have any questions, please contact me directly by phone at (314) 645-6600, ext. 2530 or fax at (314) 567-0704.

Sincerely,

A handwritten signature in dark ink, appearing to read 'Herbert G. Luther', with a stylized flourish at the end.

Herbert G. Luther, Ph.D.  
Vice President Regulatory & Clinical Affairs  
KV Pharmaceutical Company

**KV PHARMACEUTICAL COMPANY**

**ORIG AMENDMENT**

NIFA

**KV**

Certified Mail  
ML No.

September 12, 2000

Office of Generic Drugs,  
CDER, FDA  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

Re: **ANDA 75-609**  
**Doxazosin Mesylate Tablets, 1 mg, 2 mg, 4 mg, and 8 mg**  
**Telephone Amendment**

Dear Madam/Sir:

Reference is made to a telephone conversation held on September 7<sup>th</sup>, 2000. Participating in this phone conversation were: Dr. Lang Lee, reviewer, and Mrs. Elain Hu, Project Manager of the Office of Generic Drugs and Mr. Angel Rodriguez and Dr. Herb Luther of KV Pharmaceutical. FDA made two requests during this conversation:

1. To supply full term stability data for all strengths of the proposed drug product, including all packaging configurations.
2. To tighten the specification for total impurities in the drug substance.

Attached, you will find the 24-month stability data for all strengths in the 100 count container using the FDA required dissolution conditions (Q= % at 30 min), which was agreed to by KV. The 24-month stability data for the 1,000 count container could not be provided as the samples are due to be pulled from the stability chamber on October 6, 2000, according to the submitted stability protocol. KV has committed to the FDA proposed dissolution criteria, and will abide by our post approval stability commitments. In this regard, should any batch be found with out of specification results, KV shall proceed as directed by the approval conditions of this ANDA, and as per cGMP.

..., manufacturer of Doxazosin Mesylate, has already tightened their specifications for total impurities from %. However, after review, they have agreed to tighten the specification for total impurities to NMT %, but they advise that they are not able to tighten this specification further. KV has included an updated drug substance specification sheet, which reflects this change.



ANDA 75-609  
Fax Amendment – 9/12/00  
Page 2

KV wishes to satisfy the Agency's requests in the most expeditious manner possible. Should there be any other issue pertaining this drug product application, do not hesitate to contact me at your earliest convenience. KV looks forward to obtaining the approval of this application before the relevant patent expiration on October 18, 2000. Should any further information be needed, please contact me at 314-645-6600, ext. 2535, or Dr. Herb Luther at ext. 2530. Our fax number is 314-567-0704.

As usual, I thank you for your dedication on these matters.

Cordially,



Angel L. Rodriguez, RAC  
Regulatory Affairs Director



**KV PHARMACEUTICAL COMPANY**

May 22, 1999

Mr. Robert L. West, Director  
Division of Labeling and Program Support  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Metro Park North  
7500 Standish Place  
Rockville, MD 20855

**NEW CORRESP**  
**NC**

**RE: ANDA 75-609, Doxazosin Mesylate Tablets, 1 mg, 2 mg, 4 mg, and 8 mg  
Submitted as New Correspondence**

This letter is the result of the April 20, 1999 correspondence from the FDA, in which the FDA notified KV Pharmaceutical Company that the above ANDA had been accepted for filing on March 30, 1999.

In the April 20, 1999 correspondence, there were the following two requests for additional information:

1. However, in the interim, please submit three additional copies of the analytical methods and descriptive information needed to perform the tests on the samples (both the bulk active ingredient(s) and the finished dosage form) and validate the analytical methods.

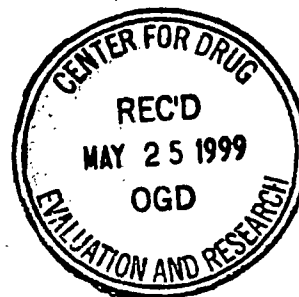
Three additional copies of the analytical methods and descriptive information for the bulk active ingredient(s) and the finished dosage form are included.

We are currently reviewing the analytical methods validation documentation that was sent with the original ANDA application. This review is not complete at this time. When this review and possible supporting activities are completed, we will forward additional information to the FDA.

2. Please provide a container label for the reference listed drug per 314.94 (a) (8).

Three (3) copies of container labels for the reference listed drug are included. They could not be removed from the bottles, so photocopies were made. In addition, three (3) copies of a side-by-side comparison of the approved container label and the proposed container label are also provided.

This letter certifies that a true copy of this correspondence is being sent to the St. Louis, Missouri FDA office for inclusion with the field copy of this ANDA.

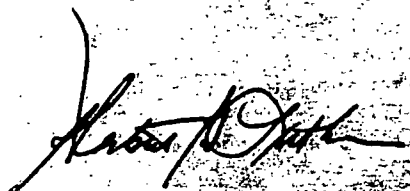


Page 2

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If further information is needed, please contact me directly by telephone at (314) 645-6600, extension 2530; or by fax at (314) 567-0704.

Sincerely,

A handwritten signature in dark ink, appearing to read "Herbert G. Luther". The signature is fluid and cursive, with a large initial "H" and "L".

Herbert G. Luther, Ph.D.  
Vice President, Regulatory & Clinical Affairs  
KV Pharmaceutical Company